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(54) PREPARATION OF TRIFLUOROMETHYL PHENOXYACETIC ACID ESTER

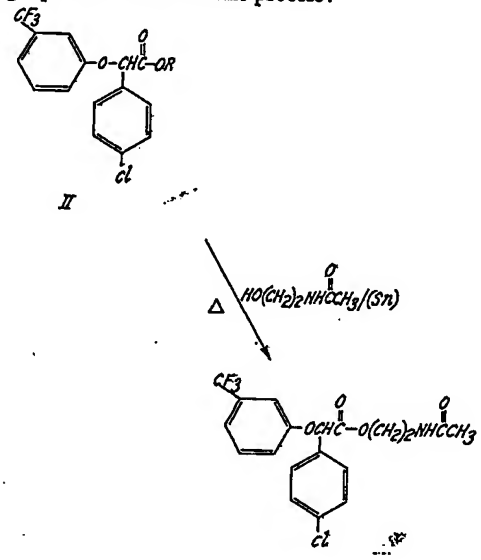
(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the preparation of 2 - acetamidoethyl(3 - trifluoromethylphenoxy)(4 - chlorophenyl)acetate.

There is no clear agreement about the actual role of cholesterol and triglycerides in the localization of atherosclerotic plaques but numerous studies support the concept that cholesterol and triglycerides play a major role in the pathogenesis of atherosclerosis because along with other lipids and fibrin they accumulate in the arterial intima and subintima and produce arterial corrosion.

2 - acetamidoethyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl) - acetate is effective in reducing the concentration of cholesterol, triglycerides and other lipids in the blood serum. This compound induces a significant reduction in cholesterol and triglyceride levels in serum and it achieves this result with little or no irritation to the gastrointestinal tract.

In accordance with this invention the C_{1-5} alkyl esters of (3 - trifluoromethylphenoxy) - (4 - chlorophenyl)acetic acids (II) are converted to 2 - acetamidoethyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl)acetate by heating with 2 - acetamidoethanol in the presence of a catalytic amount of an organo tin compound at a temperature in the range 90 to 110°C and continuously removing the C_{1-5} alkanol formed. The following equation illustrates this process:



where R is C_{1-5} alkyl, for example, methyl, ethyl, *n*-propyl, *n*-butyl or *n*-pentyl, preferably methyl. The process of the present invention can give a high yield of the desired product.

The organo tin catalysts suitable for use in this process include the trialkyl tin alkanoates, the dialkyl tin dialkanoates, the dialkyl tin sulfates or the dialkyl tin oxides, the alkyl radical being a C_{1-8} alkyl radical including methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, heptyl, octyl and branched-chain isomers thereof, and preferably being *n*-butyl radical, and the alkanoyl radicals being the corresponding radicals of the alkanoic acids containing from 2—8 carbon atoms in the molecule. The preferred organo tin catalysts include the dialkyl tin diacetates such as di-*n*-butyltin diacetate and the dialkyl tin sulfates such as di-*n*-butyltin sulfate. Also, the dialkyl tin oxides may be used, for example, dimethyltin oxide, di-*n*-butyltin oxide and dioctyltin oxide. The amount of catalyst will vary depending upon the particular catalyst but is usually from 1.0 to 8 mole % of the ester.

The solvent for the process can be an excess of 2-acetamidoethanol. In general those solvents that are inert to the reactants and have a higher boiling point than the C_{1-5} alkanol formed during the reaction will afford excellent yields since they permit the continuous removal of the C_{1-5} alkanol. The preferred solvents are aromatic solvents, for example, xylene, toluene, benzene and chlorobenzene, the preferred solvent being xylene. When a solvent is used, the reaction is conducted at reflux so that the alkanol formed may be continuously removed by fractional distillation. The temperature of the reaction is critical to the yields obtained and must be from 90° to 110°C., with 100°C. being the preferred temperature. Therefore, the pressure must be regulated so that the particular solvent will reflux at a temperature in the range of from 90° to 110°C.

For example, methyl 3 - (trifluoromethylphenoxy) - (4 - chlorophenyl) - acetate is refluxed with 2-acetamidoethanol in the presence of di-*n*-butyltin diacetate or di-*n*-butyltin sulphate in an aromatic solvent, e.g. xylene, toluene, benzene or chlorobenzene, the methanol being continuously removed. When xylene is used, in this reaction or any other, a pressure of from say 140 mm. to 260 mm. is required to cause the solvent to reflux at a temperature in the range of from 90° to 110°C., about 200 mm. giving a reflux temperature of 100°C. The reaction is generally completed in from about two to about five hours.

After completion of the transesterification reaction, the 2 - acetamidoethyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl)acetate can be recovered by standard techniques. The best method, when using an aromatic solvent such as xylene, is to wash and dry the solution, reduce the volume, seed the solution while warm and finally cool the solution to about 0°C. This recovery method affords substantially pure product which is suitable for use without further purification.

The following examples illustrate the process of this invention.

EXAMPLE 1

2-Acetamidoethyl (3-trifluoromethylphenoxy)(4-chlorophenyl)-acetate

Methyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl) - acetate (103.3 g., 0.30 mole), 2 - acetamidoethanol (46.0 g., 0.45 mole), di - *n* - butyltin diacetate (6.4 g., 0.018 mole), and xylene (300 ml.) are heated with stirring at 100°C. and approximately 200 mm. Hg pressure. Vapors from the boiling solution are fractionated and the methanol-rich xylene is split from the top of the column. After three hours' reaction time, the batch is cooled to 50°C. Xylene is added to return the batch to its original volume and benzene (300 ml.) is added to the batch. The batch is washed successively at 35°—40°C. with 500 ml. of a 5% sodium bicarbonate solution, and twice with 500 ml. water. The wet organic layer is dried by azeotropic distillation and filtered. The filtrate is concentrated to a volume of 375 ml. The product is crystallized by seeding at 55°C. and slowly cooling to 25°C. and then to —5°C. for two hours. The product is collected and dried to afford 110.8 g. (89% yield) of 2 - acetamidoethyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl)acetate, m.p. 92°—94°C.

EXAMPLE 2

2-Acetamidoethyl (3-trifluoromethylphenoxy)(4-chlorophenyl)-acetate

2 - Acetamidoethanol (45.0 g., 0.438 mole) and di - *n* - butyltin sulfate (6.0 g., 0.0182 mole) is added to xylene (100 ml.) and heated to 100°C., under a nitrogen atmosphere, to dissolve the catalyst. The solution is cooled to 50°C. and methyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl)acetate (103.25 g., 0.3 mole) and xylene

(100 ml.) added. Twenty-two inches (22") of mercury vacuum is applied and the reaction mixture heated to 100°C. with vigorous agitation. The vacuum is adjusted to maintain a reflux temperature of 100°C. The reaction mixture is refluxed with fractionation for three hours, cooled to 60°C. and diluted with xylene (500 ml.). The xylene solution is washed with water 2×1 l.) and a 5% sodium chloride solution (0.5 l.). The xylene solution is reduced in volume by 100 ml. under vacuum (to remove water), treated with charcoal and filtered. (*Note*: 200 ml. of xylene was used as a wash.) The xylene solution is vacuum distilled to a volume of 375 ml., seeded at 55°C. and cooled to 25°C. and hexane is added (375 ml.) over a one-hour period. The 2 - acetamidoethyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl)acetate is collected and dried to afford 112 g. (90% yield) of product, m.p. 92—94°C.

EXAMPLE 3

2-Acetamidoethyl (3-trifluoromethylphenoxy)(4-chlorophenyl)-acetate

Methyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl) - acetate (68.9 g., 0.20 mole), 2 - acetamidoethanol (30.0 g., 0.292 mole) and di - *n* - butyltin sulfate (4.0 g., 0.12 mole) are heated with stirring at 100°C. for 2½ hours. The methanol liberated is removed continuously by distillation under vacuum (Final pressure <1 mm. Hg). The reaction mixture is cooled, diluted with toluene (600 ml.) and the toluene solution is washed with water (1×500 ml.), a 5% sodium bicarbonate solution (1×500 ml.) and again with 1×500 ml. water. After drying the toluene solution over anhydrous magnesium sulfate and filtering, the batch is concentrated to 250 ml. seeded at 45°C. and cooled to 25°C. and further crystallized by slowly adding 250 ml. petroleum ether. The batch is cooled to 0°—5°C. and aged for two hours. The solids are filtered and washed with 100 ml. of toluene:petroleum ether (1:1) at 0°—5°C. to afford 72.8 g. (87.5% yield) of 2 - acetamidoethyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl) - acetate, m.p. 92°—94°C.

EXAMPLE 4

2-Acetamidoethyl (3-trifluoromethylphenoxy)(4-chlorophenyl)-acetate

2 - Acetamidoethanol (46.0 g., 0.445 mole) and di - *n* - butyltin diacetate (6.42 g., 0.02 mole) are dried by adding xylene (150 ml.) and removing the xylene at 70°C. at reduced pressure (29" of mercury). To these reagents is added methyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl)acetate (103.25 g., 0.30 mole) and xylene (300 ml.). The reaction mixture is heated to 100°C. at reduced pressure and reflux is obtained at 100°C. by adjusting the pressure. The xylene reflux is passed through a heat exchanger and xylene vapor is sparged into the reaction mixture. The methanol formed is continuously removed. After three hours, additional xylene is added to make up any volume loss (original volume 440 ml.). The reaction mixture is diluted with benzene (300 ml.) and washed, successively, with a 5% sodium bicarbonate solution (500 ml.) and water (2×50 ml.). The solution is dried azeotropically, filtered and then concentrated at reduced pressure to a volume of 375 ml. The solution is seeded at 55°C., aged at 40°—45°C. for one hour and slowly cooled to −5°C. The solution is aged at −5°C. for two hours. The product is collected and dried to afford 110.8 g. (88.8% yield) of substantially pure 2 - acetamidoethyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl)acetate.

Preparation of Di-*n*-butyltin Sulfate

To a solution of di - *n* - butyltin diacetate (70.2 g.) in methanol (600 ml.) is added concentrated sulfuric acid (12.0 ml.) with stirring. The mixture is aged at 50°C. for one hour and then cooled to room temperature. The di - *n* - butyltin sulfate is collected, washed with methanol (500 ml.) and dried at 50°—60°C. to afford 62.7 g. (95% yield) of product.

In view of the provisions of Section 9 of the Patents Act, we draw attention to our prior Patents Nos. 1,182,007 and 1,098,111.

WHAT WE CLAIM IS:—

1. A process for preparing 2 - acetamidoethyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl)acetate that comprises heating a C_{1-5} alkyl (3 - trifluoromethylphenoxy)-(4 - chlorophenyl) acetate with 2 - acetamidoethanol in the presence of an organo tin catalyst at a temperature in the range of from 90° to 110°C and continuously removing the C_{1-5} alkanol formed.

2. A process as claimed in claim 1 in which the amount of catalyst is from 1 to 8 molar % of the amount of the C_{1-5} alkyl (3 - trifluoromethylphenoxy)(4 - chlorophenyl)acetate.

3. A process as claimed in claim 1 or 2 in which the temperature is about 100°C.

4. A process as claimed in any one of claims 1—3 in which the organo tin catalyst is a trialkyl tin alkanoate, a dialkyl tin dialkanoate, a dialkyl tin sulphate or a dialkyl tin oxide, in which the alkyl and alkanoate radicals are C_{1-8} alkyl and C_{2-8} alkanoate radicals respectively.

5. A process as claimed in claim 4 in which the organo tin catalyst is di-*n*-butyltin diacetate.

6. A process as claimed in claim 4 in which the catalyst is di-*n*-butyltin sulphate.

7. A process as claimed in claim 5 that comprises heating methyl (3 - trifluoromethylphenoxy) - (4 - chlorophenyl)acetate with 2 - acetamidoethanol in the presence of di - *n* - butyltin diacetate at 100°C and continuously removing the methanol.

8. A process as claimed in claim 6 that comprises heating methyl (3 - trifluoromethylphenoxy) - (4 - chlorophenyl) acetate with 2 - acetamidoethanol in the presence of di-*n*-butyltin sulphate at 100°C and continuously removing the methanol.

9. A process as claimed in claim 1 that comprises heating methyl (3 - trifluoromethyl phenoxy) - (4 - chlorophenyl) acetate with 2 - acetamidoethanol in the presence of di - *n* - butyltin diacetate or di - *n* - butyltin sulphate in an aromatic solvent and continuously removing the methanol.

10. A process as claimed in claim 9 in which the solvent is xylene.

11. A process as claimed in claim 9 in which the solvent is toluene, benzene or chlorobenzene.

12. A process as claimed in claim 10 in which the methyl (3 - trifluoromethylphenoxy) - (4 - chlorophenyl) acetate is refluxed with the 2 - acetamidoethanol in the presence of di - *n* - butyltin diacetate at a temperature in the range of from 90°C to 110°C and at a pressure of 140 mm to 260 mm of mercury.

13. A process as claimed in claim 12 in which the temperature is 100°C and the pressure is 200 mm of mercury.

14. A process as claimed in claim 1 substantially as hereinbefore described in any one of the Examples.

15. 2 - Acetamidoethyl (3 - trifluoromethylphenoxy) - (4 - chlorophenyl) acetate when prepared by a process as claimed in any preceding claim or an obvious chemical equivalent of such a process.

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